Articles

Prevalence of Antimicrobial Drug–Resistant *Streptococcus pneumoniae* in Washington State

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We conducted a survey to assess the prevalence and geographic distribution of antimicrobial drug resistance among invasive isolates of *Streptococcus pneumoniae* in Washington State. Sequential sterile-site pneumococcal isolates were submitted from 13 hospital laboratories between 1 October 1995 and 30 January 1997. We serotyped 275 isolates from adults and children and determined minimum inhibitory concentrations (MIC) for commonly used antimicrobial drugs. Data were abstracted from medical records to compare differences in outcome and risk factors for infection. Of the 275 isolates, 73 (26.5%) were nonsusceptible to one or more antimicrobial drugs. Penicillin-nonsusceptible pneumococci (PNSP, MIC ≥0.1 μg/ml) accounted for 42 (15.3%) of the 275 isolates including 4 (1.5%) resistant strains (MIC ≥2 μg/ml). The 42 PNSP included serogroups 6, 9, 14, 19, and 23, all of which are represented in the 23-valent pneumococcal vaccine. PNSP were also nonsusceptible to trimethoprim/sulfamethoxazole (92.9%), erythromycin (38.1%), imipenem (28.6%), and ceftriaxone (23.8%). Forty-seven (17.1%) of the 275 isolates were multiple drug–nonsusceptible pneumococci (MDNSP). A significantly greater number of patients ≤12 years of age were infected with MDNSP compared with those >12 years. Prior use of antimicrobial drugs and an immunosuppressive disorder were risk factors for infection with PNSP. In summary, pneumococci nonsusceptible to penicillin and other antimicrobial drugs are prevalent among adults with invasive pneumococcal disease in Washington State. A large proportion of PNSP are resistant to other commonly used antimicrobial drugs. Local antibiotic susceptibility data should be considered when designing empiric treatment regimens.

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Streptococcus pneumoniae is a leading cause of bacterial pneumonia, meningitis, acute otitis media, and sinusitis worldwide. An estimated 40,000 people in the United States die each year from pneumococcal infection.[1] In most instances, treatment for suspected pneumococcal infections is begun empirically. The emergence of penicillin-nonsusceptible pneumococci (PNSP), however, has complicated treatment decisions. Penicillin-nonsusceptible *S. pneumoniae* was first isolated in Papua, New Guinea, in 1967 and has since been reported with increasing frequency in the United States, Europe, Australia, and many other areas around the world.[2–12]

Previous surveillance studies have characterized the rate of penicillin nonsusceptibility for specific communities to be 6.6% to 53%.[3–7] Although PNSP is still not reportable in the majority of US states, recent recommendations suggest basing empiric treatment on local susceptibility patterns.[13] Since data on the rate of PNSP in the Pacific Northwest have not been collected recently, this study was designed to assess the proportion and geographic distribution of invasive antimicrobial drug–resistant pneumococci in Washington State and identify risk factors for infection with PNSP, differences in clinical outcomes, and documented rates of pneumococcal vaccine use among people with invasive pneumococcal disease.

Methods

All pneumococcal isolates from normally sterile body sites (blood, cerebrospinal fluid, pleural fluid,

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control
CI = confidence interval
CNS = central nervous system
MDNSP = multiple drug–nonsusceptible pneumococci
MIC = minimum inhibitory concentration
PNSP = penicillin-nonsusceptible pneumococci
PRP = penicillin-resistant pneumococci
RR = relative risk
TMP/SMX = trimethoprim/sulfamethoxazole

peritoneal fluid, and middle ear fluid) of patients at selected hospitals in Washington State during the period from 1 October 1995 through 30 January 1997 were included in the study. Patient age, sex, specimen source, and specimen collection date were recorded. Based on periodic audits of microbiology laboratory records, hospitals were excluded from participation for failure to submit all sterile-site isolates. Participating hospitals were selected based on membership in the Northwest Pharmaceutical Research Network, a nonprofit network of health care settings collaborating in pharmaceutical outcomes research, and willingness to submit isolates. An appropriate institutional review board from each hospital approved the project.

Isolates were forwarded to the clinical laboratories of the University of Washington Medical Center, subcultured to ensure viability, and stored at −70°C in a suspension of 50% trypticase-soy-yeast extract broth and 50% fetal calf serum. Frozen isolates were thawed and cultured onto sheep blood agar plates (Heart Infusion Agar; Remel, Lenexa, KS) and incubated overnight at 35°C with ~5%–10% CO_2. Colonies were tested with 10% desoxycholate solution (Difco Laboratories, Detroit, MI). Thin smears of bacteria were prepared from a 0.8% saline suspension, air-dried, and heat-fixed. The smears were tested with the OMNI (polyvalent) pneumococcal antiserum (Statens Seruminstitut, Copenhagen, Denmark) and also for reactivity with each of nine pooled antisera to determine serogroup. Isolates that were bile-positive and displayed a colonial morphology consistent with *S. pneumoniae* were included in the study. Because the first 249 isolates were positive when tested with the OMNI antisera, further use was discontinued.

Antimicrobial susceptibility testing was conducted using a microdilution procedure. Customized minimum inhibitory concentration (MIC) plates were prepared by PML Microbiologicals (Portland, OR). The following concentrations of antimicrobials were prepared: penicillin, 0.008–4.0 µg/ml; clindamycin, 0.008–1.0 µg/ml; trimethoprim/sulfamethoxazole (TMP/SMX), 0.008/0.148–4.0/76 µg/ml; cefprozil, 0.06–32.0 µg/ml; vancomycin, 0.008–1.0 µg/ml; erythromycin, 0.008–4.0 µg/ml; ceftriaxone, 0.008–4.0 µg/ml; rifampin, 0.004–4.0 µg/ml; chloramphenicol, 0.06–8.0 µg/ml; and imipenem 0.004–1.0 µg/ml. A suspension of cells equal to that of a 0.5 McFarland turbidity standard was prepared in saline. One milliliter of the suspension was added to 29 ml sterile water and used to inoculate the microdilution plates using a disposable inoculating device purchased from PML Microbiologicals. Plates were incubated overnight at 35°C in an atmosphere containing 5%–10% CO_2. Growth in microtiter plates was read visually using a mirrored plate reader. MIC was defined as the lowest concentration of antimicrobial drug that inhibited visible growth. A quality control strain of *S. pneumoniae*, ATCC 49619, was tested simultaneously with each batch of patient isolates.

MIC values were interpreted using 1997 National Committee for Clinical Laboratory Standards (NCCLS) breakpoints (all values in µg/ml)[14]:

	Intermediate	Resistant
Penicillin	0.12–1.0	≥2.0
Clindamycin	0.5	≥1.0
TMP/SMX	1.0/19 to 2.0/38	≥4/76
Erythromycin	0.5	≥1.0
Ceftriaxone	1.0	≥2.0
Rifampin	2.0	≥4.0
Chloramphenicol	—	≥8.0
Imipenem	0.25 to 0.5	≥1.0

Nonsusceptibility was defined as an MIC at the intermediate level or higher. Multiple drug–nonsusceptible pneumococci (MDNSP) were defined as nonsusceptible to two or more antimicrobial drugs.

Data regarding risk factors for infection such as underlying diseases, location before admission, antimicrobial drug use in the previous month, and age were abstracted from the medical record. Immunosuppressed status was defined as the presence of AIDS, history of organ transplantation or lymphoma, treatment with immunosuppressive therapy, or neutropenia. Clinical outcomes such as length of hospital stay, admission to an intensive care unit (ICU), ICU length of stay, presence of complications (acute renal failure, assisted ventilation, hypotension, acute liver failure, or cardiac arrest), and mortality were assessed. Documentation of the use of the 23-valent pneumococcal vaccine was recorded. Random reliability reviews were completed on charts from each hospital by alternative abstractors to reduce interabstractor variability in data collection. All data was entered into an Epi Info data set (version 6.03; Centers for Disease Control and Prevention [CDC], Atlanta, GA) and then exported into SAS System for Windows (version 6.11) for data analysis. Relative risks (RRs) and their 95% confidence intervals (CIs) and Wilcoxon two-sample tests with a type I error level of 0.05 were used where indicated.

Results

Antimicrobial drug susceptibility data

We received 449 pneumococcal isolates from 23 hospitals during the 16-month study period. Eight hospitals submitting a total of 41 isolates were excluded from the study for failure to submit all sterile-site pneumococcal isolates,

TABLE 1.—*Antimicrobial drug nonsusceptibility for six S. pneumoniae serogroups, including nonsusceptibility to at least one antimicrobial drug and MDNSP*

		Isolates Nonsusceptible									Nonsusceptible to At Least One	
Serotype	Isolates	Penicillin (PNSP)	TMP/SMX	Erythromycin	Ceftriaxone	Imipenem	Clindamycin	Chloramphenicol	Rifampin	Vancomycin	Antimicrobial Drug	MDNSP
14	44 (16.0)	7 (15.9)	8 (18.2)	2 (4.5)	1 (2.3)	1 (2.3)	1 (2.3)	0	0	0	9 (20.5)	8 (18.2)
9	41 (14.9)	10 (24.4)	9 (22.0)	4 (9.8)	2 (4.9)	1 (2.4)	0	1 (2.4)	0	0	12 (29.3)	8 (19.5)
6	30 (10.9)	9 (30.0)	18 (60.0)	9 (30.0)	0	1 (3.3)	2 (6.7)	2 (6.7)	1 (3.3)	0	20 (66.7)	13 (43.3)
19	27 (9.8)	9 (33.3)	12 (44.4)	6 (22.2)	4 (14.8)	4 (14.8)	0	3 (11.1)	0	0	12 (44.4)	9 (33.3)
23	18 (6.5)	6 (33.3)	13 (72.2)	3 (16.7)	3 (16.7)	5 (27.8)	0	4 (22.2)	0	0	14 (77.8)	6 (33.3)
4	21 (7.6)	0	2 (9.5)	1 (4.8)	0	0	1 (4.8)	0	0	0	3 (14.3)	1 (4.8)
Other	94 (34.2)	1 (1.1)	2 (2.1)	3 (3.2)	0	0	1 (1.1)	0	0	0	5 (5.3)	2 (2.1)
Total	275	42 (15.3)	64 (23.3)	28 (10.2)	10 (3.6)	12 (4.4)	5 (1.8)	10 (3.6)	1 (0.4)	0	75 (27.3)	47 (17.1)

Data are *n* (%). Susceptibility is defined in Methods.

and 133 isolates were excluded because of nonviability, collection from a nonsterile body site, duplication, or unknown hospital source. Antimicrobial susceptibility testing and serotyping were thus performed on 275 sterile-site isolates of *S. pneumoniae* from 11 community- and 2 university-based hospitals. Five hospitals are located in Seattle, six in the greater Puget Sound region (one in Olympia, three in Tacoma, one in Puyallup, one in Everett), and one each in Yakima and Spokane.

Of the 275 isolates, 258 (93.8%) were from blood. Other sources and numbers of isolates included middle-ear fluid, 5 (1.8%); cerebrospinal fluid, 4 (1.5%); pleural fluid, 4 (1.5%); peritoneal fluid, 1 (0.4%); bone marrow, 1 (0.4%); mastoid, 1 (0.4%); and brain biopsy, 1 (0.4%). One hundred nineteen (43.3%) were from Seattle hospitals, 93 (33.8%) from the greater Puget Sound region, 40 (14.5%) from Yakima, and 23 (8.4%) from Spokane. Eleven serogroups, all within the currently available 23-valent pneumococcal polysaccharide vaccine, represented the majority (230, 83.6%) of the 275 isolates, including serogroups 14 (44, 16.0%), 9 (41, 14.9%), 6 (30, 10.9%), 19 (27, 9.8%), 4 (21, 7.6%), 23 (18, 6.5%), 22 (12, 4.4%), 12 (11, 4.0%), 18 (10, 3.6%), 1 (9, 3.3%), and 7 (7, 2.5%); 25 isolates (9.1%) could not be assigned to a serotype. The remaining 20 isolates belonged to one of the following serogroups: 3, 8, 10, 11, 13, 15, 16, 20, 31, 33, 38, and 29/35/42.

Susceptibility data are presented in Table 1. PNSP (MIC ≥0.1 µg/ml) accounted for 42 (15.3%) of the 275 isolates and included 4 (1.5%) penicillin-resistant pneumococci (PRP) (MIC ≥2 µg/ml). Serogroups 9 (10, 23.8%), 6 (9, 21.4%), 19 (9, 21.4%), 14 (7, 16.7%), and 23 (6, 14.3%) made up 41 (97.6%) of the 42 PNSP. Forty (95.2%) of the 42 PNSP isolates were nonsusceptible to at least one additional antimicrobial drug, 39 (92.9%) to TMP/SMX, 16 (38.1%) to erythromycin, 12 (28.6%) to imipenem, 10 (23.8%) to ceftriaxone, 9 (21.4%) to chloramphenicol, 1 (2.4%) to clindamycin, and 1 (2.4%) to rifampin. Thirty-three (12.0%) of the 275 isolates were susceptible to penicillin and nonsusceptible to one or more other antimicrobial drugs. There were no significant temporal differences in the prevalence of PNSP when the study period was divided into quartiles.

Seventy-five (27.3%) of the 275 isolates were nonsusceptible to at least one of the following drugs: TMP/SMX, penicillin, erythromycin, imipenem, ceftriaxone, chloramphenicol, clindamycin, and rifampin (Table 1). All 275 isolates were susceptible to vancomycin. Five serogroups (6, 23, 19, 9, 14) accounted for 67 (89.3%) of the 75 isolates nonsusceptible to at least one antimicrobial drug. Twenty (66.7%) of the 30 serogroup-6 isolates and 14 (77.8%) of the 18 serogroup-23 isolates were nonsusceptible to at least one antimicrobial drug. Thirteen (72.2%) of 18 serogroup-23 isolates and 18 (60.0%) of 30 serogroup-6 isolates were nonsusceptible to TMP/SMX, 7 (38.9%) of those solely to TMP/SMX.

Forty-seven (17.1%) of the 275 isolates were MDNSP. Serogroups 9 (8, 17.0%), 19 (9, 19.1%), 14 (8, 17.0%), 6 (13, 27.7%), and 23 (6, 12.8%) comprised 44 (93.6%) of the 47 MDNSP isolates. Forty (85.1%) of the 47 MDNSP were also PNSP (Table 1).

Demographic and risk factor data

Two hundred forty-seven (89.8%) patient medical records were available for data abstraction. Mean patient age was 48.2 years (range 1 day to 95 years). The majority of the enrolled patients were Caucasian adults with at least one underlying illness; the most common diagnosis was pneumonia (Table 2).

Fifteen (28.8%) of 52 patients ≤12 years of age were infected with MDNSP compared with 27 (13.8%) of 195 persons >12 years of age (RR 2.08; 95% CI 1.2–3.62). There were no statistically significant differences with regard to patient age and rate of resistance to individual antimicrobial drugs. There were also no statistically significant differences in either the proportion of nonsusceptible strains or serogroup distributions by geographic region.

Two variables were found by univariate analysis to be risk factors for infection with PNSP: immunosuppression and antimicrobial drug use in the month before admission.

TABLE 2.—*Demographic data for 247 patients with invasive pneumococcal infection*

Variable	Value (%)
Age (years)	
Mean (range)	48.2, 0.1–95
<2	35 (14.2)
2–12	17 (6.9)
13–40	34 (13.8)
41–64	70 (28.3)
≥65	91 (36.8)
Race	
Caucasian	115 (46.6)
African-American	14 (5.7)
Hispanic	1 (0.4)
Native American	8 (3.2)
Unknown	109 (44.1)
Sex	
Male	139 (56.3)
Female	107 (43.3)
Unknown	1 (0.4)
Payment source	
Medicare	87 (35.2)
Medicaid	50 (20.3)
Private insurance	87 (35.2)
Self-pay	6 (2.4)
Other or unknown	17 (6.9)
Admission diagnosis	
Pneumonia	140 (56.7)
Sepsis/bacteremia	24 (9.7)
Meningitis	7 (2.8)
Other	72 (29.2)
Unknown	4 (1.6)
Underlying illness	
Chronic lung disease	65 (26.3)
Diabetes	30 (12.1)
Chronic liver disease	25 (10.1)
AIDS ($CD4^+$ <500 cells/mm^3)	6 (2.4)
Immunosuppression	26 (10.5)
Splenectomy	5 (2.0)
At least one risk factor for *S. pneumoniae* infection*	194 (78.3)

*As defined by the CDC: age <2 or ≥65 years, chronic liver disease, chronic pulmonary disease, diabetes, splenectomy, or immunosuppressive conditions including HIV positivity, solid organ or bone marrow transplantation, neutropenia, and immunosuppressive drug therapy.

Nine of 26 (34.6%) immunosuppressed patients were infected with PNSP compared with 27 of 221 (12.2%) non-immunosuppressed patients (RR 2.83; 95% CI 1.5–5.35). Ten of 29 (34.5%) patients with a history of antimicrobial drug use the month before hospitalization were infected with PNSP compared with 26 of 211 (12.3%) patients not taking antimicrobial drugs (RR 2.88; 95% CI 1.55–5.34). Moreover, both immunosuppression and prior antimicrobial drug use were found by multivariate analysis to be significantly associated with infection with PNSP ($P < 0.01$ and $P < 0.02$, respectively). All other risk factors assessed (race; sex; insurance status; place of residence; alcohol or tobacco use; presence of underlying disease such as diabetes or chronic lung, renal, or liver disease; history of otitis media; or splenectomy) were not significantly related to infection with PNSP. The mean length of hospital stay for patients with a penicillin-sensitive organism was 5.7 days compared with 7.1 days for those with a nonsusceptible organism ($P = 0.47$). There was no significant difference between patients with penicillin-susceptible and penicillin-nonsusceptible isolates with respect to admission to an ICU, ICU length of stay, occurrence of complications such as requirement for mechanical ventilation or a hypotensive episode, or mortality.

Of the 247 patients whose records were available, 178 (72.1%) had evidence of clinical improvement (return of temperature to normal, decreased requirement for supplemental oxygen, or improved subjective status) upon hospital discharge, 29 (11.7%) did not show improvement, and 25 (10.1%) died. (The status of 15 (6.1%) patients was not documented.) Infection with PNSP was not associated with increased risk for lack of improvement or death.

Of the 247 patients whose records were available, 194 (78.5%) had at least one risk factor for *S. pneumoniae* infection as defined by the Advisory Committee on Immunization Practices (ACIP) (age <2 or ≥65 years; presence of chronic liver disease, chronic pulmonary disease, or diabetes; presence of an immunosuppressive condition; or splenectomy), and 160 patients (64.8%) were candidates for the 23-valent pneumococcal vaccine according to ACIP guidelines.[15] Receipt of the pneumococcal vaccine (before or during hospitalization or anticipated after discharge) was documented in the medical record for 12 (4.9%) patients.

Discussion

Drug-resistant strains of *S. pneumoniae* were relatively uncommon in the United States before the 1990s. Since then, increasing prevalence of drug-resistant organisms has been documented in numerous areas around the country.[3–6,16,17] The CDC pneumococcal sentinel surveillance system has shown an increase in both PNSP (from 6.6% to 14.1%) and PRP (from 1.3% to 2.2%) between 1992 and 1994 among invasive pneumococcal isolates collected from 13 hospitals in 12 states.[3,4]

Our study found the prevalence of PNSP to be 15.3% among isolates from 13 hospitals in Washington State, consistent with the CDC's most recent national surveillance study. This prevalence of PNSP is consistent with the suggestion that empiric treatment regimens for central nervous system (CNS) infections and life-threatening non-CNS infections caused by *S. pneumoniae* should include vancomycin in addition to an extended-spectrum cephalosporin.[18] The PRP prevalence of 1.5% in our study is lower than the national rate of 3.2% for invasive pneumococcal infections.[4] Rates of PRP in a community can increase dramatically within a short time.[6] In addition, rates of PRP may vary from hospital

to hospital, and increased proportions of PRP may exist in hospitals not represented in our study. The small proportion of penicillin-resistant isolates is encouraging, but continued local surveillance of invasive pneumococcal isolates throughout Washington State is recommended to look for increases in resistance rates that recent national and global resistance trends portend.[8,19]

Ninety-five percent of our PNSP and PRP isolates were MDNSP, while only 3% of the penicillin susceptible isolates were MDNSP. These data further support NCCLS recommendations to test the susceptibility patterns of all sterile-site isolates using the oxacillin disk diffusion screening followed by MIC testing for penicillin, as well as extended-spectrum cephalosporins and several other antimicrobial drugs that may be clinically indicated for treatment, such as erythromycin, tetracycline, TMP/SMX, vancomycin, and chloramphenicol.[14]

The majority of our study patients (56.7%) with invasive pneumococcal disease were admitted with a diagnosis of pneumonia. Treatment with intravenous penicillin G or other β-lactam drugs results in high serum concentrations that greatly exceed the current penicillin MICs.[20] In fact, available data suggest that bacteremic pneumococcal pneumonia caused by PNSP and treated with conventional β-lactam therapy does not result in increased mortality.[21] Although our study has limited power, we did not find infection with PNSP to be associated with increased morbidity or mortality. A conservative approach to β-lactam antimicrobial drug dosing (such as 2 to 4 million units of penicillin per adult dose) that will ensure concentrations above the MIC may be adequate in uncomplicated cases of non-CNS infection. Some authorities suggest using an extended-spectrum cephalosporin for severe PNSP infections.[22] For patients with β-lactam hypersensitivity, a macrolide, tetracycline, quinolone, or vancomycin is recommended depending on local resistance patterns.[20] Use of an extended-spectrum cephalosporin and vancomycin with or without rifampin has been recommended for empiric treatment of suspected PNSP meningitis.[18,23]

The results of this study are consistent with prior data demonstrating that use of antimicrobial drugs for treatment or prophylaxis is associated with antimicrobial drug resistance among *S. pneumoniae*.[24–27] An association between drug-resistant pneumococcal infection and immunosuppression has been reported previously.[28] We also found that immunosuppression was associated with drug-resistant *S. pneumoniae* infection independent of antimicrobial drug use in the past month. Possible explanations for this observation include an effect of long-term antimicrobial use among immunosuppressed patients or a dose-response relationship, with immunosuppressed patients receiving more courses of antimicrobial drugs or drugs that are more efficient at selecting resistant strains. More frequent hospitalization with nosocomial acquisition of PNSP may also be a reason for increased resistance rates among immunocompromised patients.

Five serogroups (9, 19, 14, 6, and 23) were represented among 97.6% of PNSP and 93.6% of MDNSP in our study, consistent with previous surveillance reports.[3,4] Not only are these five serogroups contained in the 23-valent pneumococcal vaccine, but the serogroups of 240 (87.3%) of the 275 isolates collected during this study are also included in the vaccine. In general, approximately 85%–90% of invasive pneumococcal infections in the United States are caused by one of the 23 capsular types found in the vaccine.[29]

Patients 2 to 12 years of age were more likely to be infected with PNSP and, along with patients ≤2 years of age, were more likely to be infected with MDNSP than patients >12 years. The 28.6% rate of resistance to at least one antimicrobial drug and the 16.5% rate of MDNSP in adults ≥65 years of age or older deserve emphasis, as consequences of treatment failure may be greater in the elderly.[4,5] For patients >60 years, the incidence of pneumococcal pneumonia is estimated to be 3 to 8 cases per 1,000 persons per year, a figure three times higher than that for younger adults. Ten to 30% of elderly patients with pneumococcal pneumonia will develop bacteremia and, despite appropriate antimicrobial treatment and intensive medical care, 30%–40% of elderly patients with pneumococcal bacteremia will die.[29] Case-control studies have shown that pneumococcal vaccination prevents invasive bacteremic disease in 56% to 81% of cases and may offer a more proactive approach for prevention of invasive pneumococcal infections.[29]

Of the 247 patients with available records, 194 (78.5%) were found to have at least one risk factor for infection with *S. pneumoniae* as defined by the CDC. Of those, 160 (82.5%) should have received the vaccine according to the ACIP guidelines,[29] but only 12 (6.2%) had medical record documentation of receipt of the vaccine before or during their hospital admission. Although medical record documentation is very likely a minimum estimate of vaccine utilization, this rate of vaccination is low, and measures previously recommended by the ACIP, such as standing orders for pneumococcal vaccination administration, standards for immunization record review, community immunization programs, joint administration with the influenza vaccine, and patient and provider education sessions to increase awareness of its benefits, should be encouraged.[29]

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